Review Article

Characteristics of the pathophysiology of type 2 diabetes in Asians

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Abstract: Asia is considered as the epicenter of recent worldwide epidemic of diabetes owing to its large population and high prevalence of diabetes. In Asia, type 1 diabetes is relatively rare in comparison with European countries. Therefore, the rapid increase in the prevalence of type 2 diabetes is the driving force of the epidemic. Interestingly, the phenotypes of Asian type 2 diabetes are distinct as compared by non-Asians, particularly Caucasians. Asian type 2 diabetes patients are generally non-obese, have a prominent impairment in insulin secretion and a better insulin sensitivity than non-Asians. Whereas incretin effect is remarkably reduced in European patients with type 2 diabetes, Asian patients with type 2 diabetes exhibited a similar incretin effect compared to non-diabetic subjects. Type 2 diabetes diagnosed by isolated postprandial hyperglycemia is more common in Asia than in Europe. Interestingly, glucose lowering efficacy is greater in Asians than in non-Asians. Genetic backgrounds in both nuclear and mitochondrial genome are different among ethnic groups, which may contribute to unique features of type 2 diabetes found in Asians. Considering the differences in pathophysiology and clinical features of Asian type 2 diabetes, we need to use different approach in diagnosis and management of type 2 diabetes including selecting patients eligible for bariatric/metabolic surgery.

Keywords: Asian; type 2 diabetes mellitus; pathophysiology; insulin secretion; insulin sensitivity

Received: 04 December 2016; Accepted: 20 December 2016; Published: 08 February 2017.
doi: 10.21037/ales.2017.01.03
View this article at: http://dx.doi.org/10.21037/ales.2017.01.03

Introduction

Asia, where 60% of world population live, is the epicenter of the current worldwide epidemic of diabetes. Because type 1 diabetes is relatively rare in Asia compared to Western countries, the driving force of recent diabetes epidemic in Asia is the steep increase in the prevalence of type 2 diabetes. Type 2 diabetes is a result of the interplay among multiple genetic and environmental factors. Considering that Asians have different genetic backgrounds and culture including food and other lifestyle factors, it is not surprising that they have different characteristics of type 2 diabetes. In addition, the differences in pathophysiology of type 2 diabetes may result in different responses to anti-diabetes drugs compared to other ethnic groups. In the same line, increasing evidence suggests that the cutoff for body mass index (BMI) for bariatric/metabolic surgery needs to be reduced in Asians.

Characteristics of the pathophysiology of Asian type 2 diabetes

A lower BMI

Prevalence of obesity, which is defined by a BMI cutoff of 30 kg/m^2, is approximately 30% in diabetes patient in the US (1). Notably, the prevalence of obesity in East Asian diabetes patients is only 3–4% (1). However, the prevalence of diabetes between the US and East Asia is similar, around 8% (1). The precise mechanism of increased diabetes risk in spite of a lower BMI in East Asians is not clearly understood. Intriguingly, East Asians have a higher visceral fat area, which is related to insulin resistance, at a given waist circumference than in Caucasians (2,3). In a cross-sectional study of 490,288 UK Biobank participants including 1,534 Chinese, a BMI cutoff of 24.0 kg/m^2 for Chinese women and 26.0 kg/m^2 for Chinese men was

estimated to show a similar prevalence of diabetes at a BMI cutoff of 30 kg/m^2 for white people (4). The equivalent waist circumference for a same prevalence of diabetes was 88 and 74 cm in white and Chinese women; 102 and 88 cm in white and Chinese men, respectively (4). Further studies are necessary to elucidate the mechanism of increased diabetes risk at a lower degree of obesity in Asians.

Impaired insulin secretion rather than insulin resistance is the major defect

From an insulinocentric view point, type 2 diabetes is a result of the interplay of insulin secretion and action. A meta-analysis compared insulin sensitivity and acute insulin response during frequently sampled intravenous glucose tolerance tests in Africans, Caucasians, and East Asians (5), showed a higher insulin sensitivity and a lower acute insulin response in East Asians than other races across all glucose tolerance categories [normal glucose tolerance (NGT), impaired glucose regulation, and type 2 diabetes].

In a prospective cohort study with a median follow-up duration of 9.7 years (Whitehall II study), which included 6,538 British civil servants without diabetes at baseline, insulin sensitivity decreased during the 5 years before the onset of diabetes whereas beta-cell function increased 3–4 years before the onset and thereafter decreased in a rapid pace (6). In this study, insulin sensitivity and beta-cell function were estimated by the homeostasis model assessment (HOMA) methods, which use fasting plasma insulin and glucose levels. The biphasic beta-cell response to decreasing insulin sensitivity observed in this study suggests a compensatory effort of pancreatic beta-cells to meet the increased insulin demand to overcome prevailing insulin resistance, which is not sustainable over a long period of time for people who develop diabetes.

Our group also followed up 4,106 Koran subjects with NGT for 10 years with biennial oral glucose tolerance tests (OGTT) (the Korean Genome and Epidemiology Study) (7). Pancreatic beta-cell function and insulin sensitivity were estimated by the 60-min insulinogenic index and composite insulin sensitivity index (Matsuda index), which utilize both fasting and post-challenge levels of glucose and insulin during the OGTT. At baseline, even though all the subjects had NGT, beta-cell function was lower by 35.4% and insulin sensitivity was also lower by 18.0% in subjects who developed diabetes than in those who remained as NGT. Those who remained as NGT showed a decline in insulin sensitivity but they showed a compensatory increase in beta-cell function (7). In contrast, those who developed diabetes also showed a decline in insulin sensitivity over the 10-year time period. However, they did not show such compensatory increase in beta-cell function (7). Therefore, most Korean people who develop type 2 diabetes do not exhibit beta-cell compensation to meet the increased demand for insulin with decreasing insulin sensitivity over time.

Despite the striking differences in insulin secretion and insulin sensitivity between Caucasians and East Asians, direct comparison in a large scale has been done only recently. A cross-sectional study with 120 Japanese (mean BMI was 25.0 kg/m^2) and 150 Europeans (mean BMI was 30.8 kg/m^2) with NGT, impaired glucose tolerance (IGT), and type 2 diabetes, 5-hour OGTTs with the same protocol and the same analytic methods were performed (8). As was shown in other previous studies, Japanese subjects exhibited a higher insulin sensitivity, which was assessed by HOMA insulin resistance and Matsuda index, and a lower insulin secretory capacity, which was assessed by 30-min insulinogenic index and HOMA beta-cell function, than Europeans. However, after adjusting the difference in BMI between the two ethnic groups, all these indices of beta-cell function and insulin sensitivity became comparable, which indicated that the BMI is a main determinant of the differences in those indices between Japanese and Europeans. Intriguingly, the disposition index (the product of insulinogenic index and Matsuda index), which indicates the beta-cell function considering insulin sensitivity, was comparable between Japanese and Europeans. Therefore, it is conceivable that the apparently lower beta-cell function is appropriate for the higher insulin sensitivity in Japanese to maintain normal glucose homeostasis. However, it is unknown whether Japanese or other East Asian people can further increase beta-cell function to maintain NGT when they have a higher insulin resistance similar to Europeans.

Morphometric quantification of beta-cell area from pathology specimens in Korea (9) and Japan (10) showed that beta-cell mass was reduced in patients with type 2 diabetes compared to non-diabetic controls. In association with decreased beta-cell mass, increased alpha-cell mass (9) and increased oxidative stress (10) were noted in the pancreas of type 2 diabetes. In a Chinese autopsy study with 235 patients with type 2 diabetes and 533 non-diabetic subjects, islet amyloid deposits and pancreatic arteriosclerosis were more frequently found in patients with type 2 diabetes (11). However, whether beta-cell mass is lower in Asians than in Caucasians has not been directly evaluated.

Postprandial hyperglycemia

Comparing the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) (12) and the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) (13) study, postprandial hyperglycemia is more common in Asians than in Caucasians. The prevalence of isolated postprandial hyperglycemia was 37% and 30% in DECODA and DECODE, respectively, whereas the prevalence of isolated impaired fasting glucose was 18% and 35% in DECODA and DECODE, respectively. In addition, more than half the patients with diabetes in the DECODA study was diagnosed by isolated postprandial hyperglycemia (14). The mechanism of prominent postprandial hyperglycemia found in Asians needs to be elucidated. However, it can be partly explained by the fact that both dynamic and static beta-cell responses during the OGTT are lower in Asians than in Caucasians (15). To explain the difference in postprandial glucose control, hepatic glucose production after glucose challenge should be compared between Asians and Caucasians.

Preserved incretin effect

We have two incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (16-18). GIP and GLP-1 are secreted from enteroendocrine cells such as K-cells and L-cells, respectively, in response to absorption of glucose, fatty acids, and amino acids from the gut lumen. Thereafter, GIP and GLP-1 augment insulin secretion from pancreatic beta-cells triggered by hyperglycemia. In the past, decreased GLP-1 secretion was considered a contributing factor for the development of type 2 diabetes based on findings from earlier studies (19). However, a meta-analysis revealed that GLP-1 secretion is not decreased in type 2 diabetes (20). In addition, there is no evidence of altered GIP secretion in type 2 diabetes as shown in another meta-analysis (21). In East Asians, postprandial plasma levels of GLP-1 and GIP are also comparable between NGT and type 2 diabetes [reviewed in ref (22)].

The incretin effect is defined as the contribution of the gastrointestinal tract to postprandial insulin secretion in response to oral glucose challenge, which can be measured by two ways. Firstly, isoglycemic intravenous glucose infusion (IIGI), which reproduces the glucose excursion during the OGTT, is the gold standard method to measure incretin effect (23). Given the plasma glucose levels are identical (isoglycemic), the proportion of insulin secretion triggered by the gastrointestinal absorption of glucose can be calculated by subtracting insulin secretion during the IIGI from insulin secretion during the OGTT. Secondly, the hyperglycemic clamp with oral glucose challenge is the other option (24). After achieving steady state hyperglycemia at a certain plasma glucose level, 75 g of glucose is administered orally. By adjusting the glucose infusion rate, the plasma glucose levels can be maintained at the same steady state level after the glucose challenge. Because the plasma glucose levels are the same before and after the oral glucose challenge, we can estimate the effect of oral ingestion of glucose on insulin secretion by comparing the two different phases. In Europeans, the incretin effect measured by the IIGI method was consistently decreased in type 2 diabetes (10–40%) as compared by NGT (50–70%) (25-29). However, in Koreans (23) and Japanese (30), there is no difference in the incretin effect measured by the IIGI method between type 2 diabetes and NGT. With the hyperglycemic clamp with oral glucose challenge, there was no difference in the incretin effect between NGT and type 2 diabetes in Koreans (24). The mechanism of the discrepant results in terms of incretin effect between Asians and Caucasians may be partly explained by genetic factors (22), but further studies are warranted.

The lack of difference in the incretin effect between NGT and type 2 diabetes observed in Asians does not necessarily mean that there is no difference in the contribution of the gastrointestinal tract to postprandial glucose metabolism between NGT and type 2 diabetes. Whereas the incretin effect addresses the insulin secretion during the OGTT, the relatively new concept called gastrointestinally-mediated glucose disposal (GIGD) deals with the gastrointestinal contribution to the glucose homeostasis during the OGTT, which is calculated by the data from the OGTT and corresponding IIGI (31). Although there was no difference in the incretin effect between Korean subjects with NGT and type 2 diabetes (23), the GIGD during the OGTT was remarkably decreased in type 2 diabetes (~30%) as compared to NGT (~60%) in the same Korean study (23). In addition, the incretin effect is not an equivalent term to the effect of GLP-1 or GIP. We found the effect of intravenous GLP-1 infusion on insulin secretion during a hyperglycemic clamp is remarkably decreased in Korean subjects with type 2 diabetes compared to those with NGT (unpublished data).

Table 1 Summary of pathophysiologic characteristics of Asian type 2 diabetes

Body habitus
Commonly non-obese
More visceral fat at a given waist circumference
Insulin secretion
Lower than Caucasians
Lack of compensatory hyperinsulinemia against insulin resistance
Reduced beta-cell mass (?)
Insulin sensitivity
Better than Caucasians
Glucose tolerance
Isolated postprandial hyperglycemia is common
Incretin system
Incretin secretion: not decreased
Incretin effect: not decreased
Gastrointestinally-mediated glucose disposal: reduced
Greater efficacy of incretin-based therapies
Genetics
Different risk allele frequencies of some diabetogenic genes
mtDNA polymorphisms unique to Asian type 2 diabetes (e.g., haplogroup F)

Intriguingly, the glucose-lowering response to incretin-based therapies for type 2 diabetes such as dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists are generally greater in Asians than in non-Asians (32,33). However, this notion cannot be supported by the contradicting observations such as preserved incretin effect, preserved incretin secretion, decreased GIGD, and decreased insulinotropic effect of GLP-1 in Asian patients with type 2 diabetes, as explained above. Rather, the greater glucose-lowering efficacy of incretin-based therapies in Asians than in non-Asians can be explained by better insulin sensitivity and a lower BMI (22).

Genetic differences

With innovative advance in genotyping technology, the genetic landscape of type 2 diabetes has been largely revealed. In a trans-ancestry meta-analysis on genome-wide association studies performed in East Asians, South Asians, Europeans, and Mexican Americans exhibited similarities and differences in genetic makeups of type 2 diabetes among different ethnic groups (34). Among them, the risk allele frequency of a variant (rs7903146) in TCF7L2, a well-known type 2 diabetes gene, showed a striking difference between East Asians (5%) and Europeans (30%). Interestingly, TCF7L2 plays an important role in modulating beta-cell responses to GLP-1 and GIP by regulating the gene expression of respective receptors (35-39). Aside from nuclear DNA variants, mitochondrial DNA (mtDNA) polymorphisms/mutations are also important in conveying the susceptibility to diabetes as exemplified by mtDNA A3243G mutation (40) and mtDNA T16189C polymorphism (41). Because mtDNA is inherited exclusively through the maternal lineage and highly variable compared to nuclear DNA, it is a useful tool to explore the human migration out of Africa in prehistoric age. Highly variable mtDNAs can be grouped as mtDNA haplogroups, which show clear differences among ethnic groups. Although common mtDNAs are not associated with type 2 diabetes in Europeans (42), common Asian mtDNA haplogroups such as N9a, D5 and F confer susceptibility to type 2 diabetes in Koreans and Japanese (43). However, N9a, D5 and F did not show any apparent effects on mitochondrial function in a study with a cybrid cell system *in vitro* (44). Therefore, they may confer susceptibility to type 2 diabetes in a very complicated way influenced by other genetic and environmental factors (45). Taken together, differences in both nuclear and mitochondrial genome may contribute to the unique phenotype of Asian type 2 diabetes.

Conclusions

As explained in this review (*Table 1*), the phenotype of Asian type 2 diabetes is unique in comparison with that of non-Asians, particularly European descendants. Therefore, the different ethnic background should be considered in diagnosis and treatment of patients with type 2 diabetes. For example, most non-obese patients with diabetes have type 2 diabetes rather than type 1 diabetes and they can be effectively and safely managed with incretin-based therapies. Recent guidelines on bariatric/metabolic surgery recommend a lower BMI criteria for Asians. It is recommended that bariatric/metabolic surgery for patients with type 2 diabetes should be considered in cases with a BMI of 35 kg/m^2 or more or in cases with a BMI between

30 and 35 kg/m^2 and poor glycemic control despite medical treatment. For Asians, it is recommended that the BMI criteria can be lowered by 2.5 kg/m^2 based on the clinical differences of type 2 diabetes among ethnic groups (46-48). Further studies are required to elucidate the underlying mechanisms of ethnic differences of the phenotypes of type 2 diabetes, which will improve personalized approach in the management of type 2 diabetes.

Acknowledgments

Funding: This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI14C1277).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Wei-Jei Lee) for the series "Laparoscopic Metabolic Surgery for the Treatment of Type 2 Diabetes in Asia" published in *Annals of Laparoscopic and Endoscopic Surgery*. The article has undergone external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ales.2017.01.03). The series "Laparoscopic Metabolic Surgery for the Treatment of Type 2 Diabetes in Asia" was commissioned by the editorial office without any funding or sponsorship. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/ales.2017.01.03
Cite this article as: Cho YM. Characteristics of the pathophysiology of type 2 diabetes in Asians. Ann Laparosc Endosc Surg 2017;2:14.

